REMARKS

Paragraph numbers below refer to the Substitute Specification (clean copy) submitted on April 3, 2008.

Claims 1–16, 18 and 20–25 are pending in the present application. Claims 17 and 19 were canceled by an earlier amendment.

Claim 1 is amended for clarity by moving the recitation "partly or completely dissolved" into a separate "wherein" clause from the recitations "dispersed" and "melted".

No increase in total claim number or in number of independent claims results from the present amendment and no additional claim fees are believed payable.

No new matter is added and no change in inventorship results from the present amendment.

RESPONSE TO OFFICE ACTION DATED JUNE 24, 2008

1. Obviousness-type double patenting

Claims 1–16, 18 and 20–25 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 28–59 of copending application Serial No. 10/523,908.

The rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the co-pending application issues as a patent.

2. Rejection under 35 U.S.C. §112, first paragraph

Claims 1–16, 18 and 20–25 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement.

2.1. Claim 10

With respect to Claim 10, it is alleged that the specification does not provide support for the limitations "hydrophilic and amphiphilic polymers" and "hydrophilic and amphiphilic copolymers." This rejection is respectfully traversed, based once again on the analysis submitted in the previous response dated September 16, 2008. The Examiner indicates (Action, p. 9, line 8) that she is unable to understand this analysis. Applicant therefore

attempts, in the interest of advancing prosecution, to articulate the analysis in different words, as follows.

1. It is well accepted in U.S. claim-drafting practice that a Markush group preceded by the words "selected from the group consisting of" requires "and" as the separator between members of the group. See MPEP 2173.05(h). Applicant believes it was proper to modify the language found in the specification (which was originally filed in the German language) in accordance with good U.S. claim-drafting practice.
2. To simplify, consider option (a) as set forth in paragraph **[0076]** of the specification. It would clearly be improper to define a claim element as "an internal-phase component selected from the group consisting of hydrophilic polymers or amphiphilic polymers." Hydrophilic polymers and amphiphilic polymers are equally members of the Markush group from which the internal-phase component can be selected. The expression "an internal-phase component selected from the group consisting of hydrophilic and amphiphilic polymers" could be rephrased as "an internal-phase component wherein said component is a hydrophilic or amphiphilic polymer" without change in meaning. MPEP 2173.05(h). Applicant prefers not to rephrase in this way as it would result in more unwieldy claim language when all options set forth in paragraph **[0076]** are included.
3. It is well established that the conjunction "or" between items A and B does not exclude the presence of both A and B, unless there is express disclosure requiring that one and only one of these items is present. Indeed, familiar Boolean logic demands that "A or B" be read to cover each of the options A, B and A+B. This is the essence of Applicant's analysis in reading paragraph **[0076]** to embrace the possibility that the TTS can comprise a hydrophilic polymer, an amphiphilic polymer, or both.

Further, paragraph **[0076]** recites:

> The internal-phase components are preferably selected out of the group of
> (a) hydrophilic or amphiphilic polymers,
> (b) hydrophilic or amphiphilic copolymers,
> (c) mixtures of (a) and/or (b) with pharmaceutically acceptable softeners,
> (d) condensates from glycerin with fatty acids or polyols, and
> (e) suitable mixtures of the substances (a)–(d).

As option (e) includes mixtures of (a)–(d), the above disclosure clearly embraces a mixture of (a) and (c). Now let (a) be a hydrophilic polymer and (c) a mixture of an amphiphilic polymer with a softener. The mixture of (a) + (c), which is permitted by (e), would in this instance contain a hydrophilic polymer and an amphiphilic polymer (and a softener). It clearly being an option therefore to have both types present along with a softener, it would be a perverse interpretation of paragraph **[0076]** to assert that both types cannot be present in absence of a softener.

The same analysis can be repeated for "hydrophilic and amphiphilic copolymers."

Consequently, the specification provides adequate written description to support Claim 10 as presented. Withdrawal of the present rejection of Claim 10 under 35 U.S.C. §112, first paragraph is respectfully requested.

2.2. Claims 1–16

With respect to Claim 1, it is alleged that the specification does not provide support for the limitation "the active substance is ... melted using a hot-melt process." This rejection is respectfully traversed. Support for melting of rotigotine using a hot-melt process or method is found throughout the specification as filed, for example at paragraphs **[0109]**–**[0110]** which read (emphasis added):

> Therefore, one aspect of the invention is the use of rotigotine in the production of a TTS, characterized in that the rotigotine is infused in the cement layer of the TTS by the hot-melt method.
>
> It is entirely possible to introduce the rotigotine in the matrix either premelted or by metering it in solid form into the hot matrix melt where it is melted.

Withdrawal of the present rejection of Claims 1 and of Claims 2–26 dependent therefrom under 35 U.S.C. §112, first paragraph is respectfully requested.

2.3. Claims 18 and 20–25

No basis for rejection of Claims 18 and 20–25 under 35 U.S.C. §112, first paragraph is articulated in the present Action. The allegedly unsupported recitations of Claim 10 and of Claim 1, responded to above, are not present in any of Claims 18 or 20–25. Withdrawal of the present rejection of Claims 18 and 20–25 under 35 U.S.C. §112, first paragraph is therefore respectfully requested.

3. Rejection under 35 U.S.C. §112, second paragraph

Claims 1–16, 18 and 20–25 are rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

3.1. Claims 1–16

With respect to Claim 1, the Examiner finds the phrase "the active substance is dispersed and partly or completely dissolved and melted using a hot-melt process" to be confusing, and asks "whether the active agent is dispersed, dissolved or melted" (Action, p. 4, last paragraph). By amendment herein, the words "partly or completely dissolved" are moved out of the cited phrase to a separate "wherein" clause. It is believed that any possibility of confusion is thereby removed. It will now be clearer that, in the process for preparing the TTS, the active agent is both dispersed and melted (though not necessarily in that order – see paragraph **[0110]** of the specification), and that in the TTS the active agent is in a partly or completely dissolved state in the adhesive.

Withdrawal of the present rejection of Claim 1 and of Claims 2–16 dependent therefrom under 35 U.S.C. §112, second paragraph is respectfully requested.

3.2. Claims 18 and 20–25

No basis for rejection of Claims 18 and 20–25 under 35 U.S.C. §112, second paragraph is articulated in the present Action. The allegedly confusing phrase in Claim 1, responded to above, does not appear in any of Claims 18 or 20–25. Withdrawal of the present rejection of Claims 18 and 20–25 under 35 U.S.C. §112, second paragraph is therefore respectfully requested.

4. Rejection under 35 U.S.C. §103(a) over Chen in view of Metman and Loper

Claims 1–3, 6–16, 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,807,570 ("Chen"), in view of Metman *et al.* (2001) Clinical Neuropharmacology 24:163–169 ("Metman") and U.S. Patent No. 4,880,633 ("Loper"). This rejection is respectfully traversed.

The combination of Chen, Metman and Loper cannot establish a *prima facie* case of obviousness for independent Claims 1, 18 and 20 since in each case the combination is missing at least one of the claimed features. In particular, the cited combination fails to teach or suggest the present hot-melt process, or a product prepared thereby, wherein rotigotine is dispersed and melted to form the resultant cement matrix found in the TTS of Claim 1 and according to the methods of Claims 18 and 20. Moreover, no apparent rationale based on either the cited documents themselves or the general knowledge in the art is provided by which a skilled artisan would be led to include the missing subject matter. For at least these reasons, discussed in greater detail below, the claims are not obvious and are patentable over the cited art.

Chen proposes a transdermal system for delivery of ropinirole, comprising a laminated composite of a backing layer and a contact adhesive layer containing the ropinirole (col. 3, lines 23–38). Chen fails to teach or suggest rotigotine. Chen also fails to teach or suggest a cement matrix comprising a hot-meltable adhesive. Even if the adhesives mentioned at col. 8, lines 59–67 include some that are conceivably hot-meltable, no selection of hot-meltable types is proposed by Chen. Chen further fails to teach or suggest a process comprising melting the active substance in the adhesive. In this regard it is pointed out that in view of the very high melting point of ropinirole (approximately 247°C – see col. 2, lines 20–21), it is unlikely that melting the drug is feasible in constructing a ropinirole transdermal system according to Chen. With particular respect to instant Claims 18 and 20, as well as dependent Claim 2, Chen (col. 9, lines 39–50) proposes using a solvent – water and/or other hydrophilic solvent – to dissolve the drug, which is expressly counter to the "solvent-free" rcitations of these claims.

Metman is cited as teaching that rotigotine can be delivered transdermally for treatment of Parkinson's disease.

Loper proposes a multilaminate transdermal system containing dissolved drug in a reservoir (col. 2, lines 12–16 and 27–32). The reservoir layer comprises the dissolved drug in a continuous matrix selected from a number of polymers (col. 4, line 47 – col. 5, line 9), and can be prepared by coating the reservoir matrix material onto backing material using hot-melt deposition (col. 8, lines 27–29). However, Loper is silent regarding melting the drug in conjunction with adhesive using a hot-melt process. Instead, the Loper process appears to require that the coating material be a solution of the drug and matrix material (col. 8, lines 21–23). As the drug is in solution, the drug cannot be said to be "melted". Furthermore, no indication is given by Loper that hot-melt deposition is carried out at a temperature above the melting point of the drug.

Thus Chen, even in view of Metman and Loper, fails to teach or suggest a method, or product made by such method, in which rotigotine as active substance is dispersed and melted using a hot-melt process. In particular, the combination of documents cited in the present rejection fails to teach or suggest infusing or dispersing any active substance, rotigotine or otherwise, wherein the active substance is melted. Thus, even if a skilled artisan attempted to combine the various disclosures of Chen, Metman and Loper (no admission is made herein that motivation would have existed for such combination), the combination would not provide all the features of the present claims.

The cited documents also fail to provide an apparent rationale by which the skilled artisan would modify the collective disclosures to include the missing subject matter, and no rationale based on the general knowledge in the art is identified by which a skilled artisan would be led to include the missing subject matter. Even considering that the reservoir matrix material of Loper may be coated onto the backing material using hot-melt deposition, there is no suggestion or apparent reason for the skilled artisan to forgo first dissolving the drug and instead melt the drug.

Only the present specification and claims provide a cement matrix comprising a hot-meltable adhesive in which the active substance (rotigotine) is dispersed and melted using a hot-melt process. And only Applicant has demonstrated the benefits and surprising results that arise when rotigotine is melted in such a process.

For example, it was surprising to the present inventors that rotigotine lends itself to

processing by the hot-melt method in that it remains stable under short-term heating to temperatures up to at least 160°C and, further, that it is released from matrices prepared in this way in a continuous fashion and at a therapeutically desirable rate (specification, paragraph **[0026]**). What is more, although rotigotine is known to be susceptible to oxidation, it remains stable in the hot-melt process and is present in the resulting matrix at a purity level that is routinely better than 98% and generally over 99% (measured at 220 nm and 272 nm by HPLC; see paragraphs **[0027]** and **[0108]** and Tables 2, 3 and 4). The present compositions and methods protect rotigotine from critical environmental factors, such as light and oxygen, and can include higher rotigotine concentrations than are possible in compositions prepared by solvent-based processes; furthermore the present invention provides improved safety and processing times (paragraphs **[0028]** and **[0030]**).

Independent Claims 1, 18 and 20, and all claims dependent directly or ultimately therefrom, are for reasons set forth above not obvious over the cited combination of documents. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Metman and Loper is respectfully requested.

5. Rejection under 35 U.S.C. §103(a) over Chen in view of Metman, Loper and Noel

Claims 1–16, 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Chen in view of Metman, Loper and U.S. Patent No. RE 36,754 ("Noel"). This rejection is respectfully traversed.

The combination of the Chen, Metman, Loper and Noel references cannot establish a *prima facie* case of obviousness for independent Claims 1, 18 and 20 since in each case the combination is missing at least one of the claimed features. In particular, the cited combination fails to teach or suggest the present hot-melt process, or a product prepared thereby, wherein rotigotine is dispersed and melted to form the resultant cement matrix found in the TTS of Claim 1 and according to the methods of Claims 18 and 20. Moreover, no apparent rationale based on either the cited documents themselves or the general knowledge in the art is provided by which a skilled artisan would be led to include the missing subject matter. For at least these reasons, discussed in greater detail below, the claims are not obvious and are patentable over the cited art.

The failure of a three-way combination of Chen, Metman and Loper to establish *prima facie* obviousness of the present claims is shown above. Addition of Noel fails to cure the shortcomings of the three-way combination, and, what is more, the Chen and Noel disclosures are incompatible and cannot be properly combined as no reason is provided as to how a skilled artisan would reconcile their disparate teachings.

Noel is cited as teaching a hot-melt silicone pressure sensitive adhesive (PSA) containing organic wax. Noel discloses that hot-melt PSAs are preferred over other adhesives because no solvents are required to coat the adhesive on a substrate, such as a bandage or patch (col. 2, line 66 – col. 3, line 1). Organic waxes include mineral waxes such as ozokerite and ceresine (col. 4, line 65 – col. 5, line 3). However, Noel simply states that the hot-melt silicone PSA is suitable for assisting in delivering a bioactive agent such as a drug, but, in common with each of the other cited documents, is silent regarding the present hot-melt process wherein the active substance is dispersed and melted in the hot-meltable adhesive.

Thus Chen, even in view of Metman, Loper and Noel, fails to teach or suggest a method, or product made by such method, in which rotigotine as active substance is dispersed and melted using a hot-melt process. In particular, the combination of documents cited in the present rejection fails to teach or suggest infusing or dispersing <u>any</u> active substance, rotigotine or otherwise, wherein the active substance is melted. Thus, even if a skilled artisan attempted to combine the various disclosures of Chen, Metman, Loper and Noel (no admission is made herein that motivation would have existed for such combination), the combination would not provide all the features of the present claims.

The combination also fails to provide an apparent rationale by which a skilled artisan would modify the collective teachings to include the missing subject matter, and no reason based on the general knowledge in the art is identified by which a skilled artisan would be led to include the missing subject matter.

In addition, Chen's use of ropinirole dissolved in water or other solvent and mixed with a polymer to form a reservoir layer is at odds with Noel's preference for using a solvent-free composition and the benefits attributed by Noel to the hot-melt silicone PSA. It is not clear how a person of ordinary skill would reconcile these disparate teachings without contravening the operation of one of these references. Only the present specification and

claims appreciate the surprising result that rotigotine remains stable in admixture with molten adhesive after the drug is melted (present specification, paragraph **[0108]**).

Independent Claims 1, 18 and 20, and all claims dependent directly or ultimately therefrom, are for reasons set forth above not obvious over the cited combination of documents. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Metman, Loper and Noel is respectfully requested.

6. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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